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Drug-Eluting Compared With Bare-Metal Coronary Stents Among Elderly Patients

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Objectives We sought to determine whether drug-eluting stents (DES) were associated with improved clinical outcomes compared with bare-metal stents (BMS) among a nationally representative, nonexperimental elderly patient cohort.

Background Randomized controlled clinical trials comparing DES and BMS for treatment of coronary artery disease indicate that although the use of DES reduces rates of coronary restenosis after percutaneous coronary intervention, it does not reduce the rates of mortality or acute myocardial infarction (AMI). Nevertheless, clinical outcomes of DES in nonexperimental, routine clinical practice are uncertain.

Methods We assembled a retrospective cohort of elderly Medicare beneficiaries (n = 76,525) who received DES within 9 months after Food and Drug Administration approval of the sirolimus-eluting stent (April 2003 to December 2003). Using propensity score methods, we assembled 2 matched control cohorts who received BMS from July 2002 to March 2003 (historical controls) or from April 2003 to December 2003 (contemporary controls). Patient enrollment and claims records were obtained through December 2005 to ascertain mortality, hospitalization for AMI, and subsequent coronary revascularization.

Results Receipt of a DES was associated with a significant survival benefit, with an adjusted mortality hazard ratio of 0.83 (95% confidence interval 0.81 to 0.86) compared with contemporary controls, and a hazard ratio of 0.79 (95% confidence interval 0.77 to 0.81) compared with historical controls (control group heterogeneity: $p < 0.001$). Patients with DES had significantly lower adjusted rates of revascularization procedures within the first 2 years after PCI and lower hospitalization rates for subsequent AMI.

Conclusions In contrast to clinical trial results, DES receipt was associated with fewer subsequent revascularization procedures, lower rates of hospitalization for AMI, and improved survival among elderly Medicare beneficiaries. (J Am Coll Cardiol 2008;51:2017–24) © 2008 by the American College of Cardiology Foundation

The first drug-eluting (coronary) stents (DES) used in routine clinical practice in the U.S.—sirolimus-eluting stents—received initial Food and Drug Administration (FDA) approval in April 2003 (1). Adoption of this new technology, augmented by the approval of the paclitaxel-eluting stent in March 2004, was rapid and widespread, such that the majority of percutaneous coronary intervention (PCI) procedures in the U.S. now use 1 of the 2 FDA-approved DES (2,3), and the annual market for DES in the U.S. alone has reached $5.3 billion (4). Despite the rapid diffusion and widespread acceptance of this new technology, the clinical effectiveness of DES compared with the less-expensive bare-metal (coronary) stents (BMS) remains uncertain, particularly when coronary stents are used in routine, nonexperimental clinical settings.

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The authors of numerous randomized controlled clinical trials have consistently demonstrated that the use of DES reduces the rate of target lesion revascularization (i.e., the need to perform a repeat interventional procedure on a coronary stenosis that had recurred at the site of the initial stenting) compared with BMS, but DES do not reduce subsequent rates of major adverse clinical events or mortality (5–7). More recently, reports from clinical registries and clinical trial consortiums with longer-term follow-up data have suggested the possibility of a higher rate of late

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Abbreviations and Acronyms

AMI = acute myocardial infarction
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
FDA = Food and Drug Administration
PCI = percutaneous coronary intervention

stent failures—in particular, stent thrombosis—for patients receiving DES, which might further diminish the relative benefit of DES (8–10). Extrapolating clinical trial results to nonexperimental settings has been further complicated by the diverse clinical indications for which DES are currently used. It has been estimated that approximately 60% of drug-eluting stent use in the U.S. has been "off label," that is, used in patients with clinical conditions that do not precisely fit the FDA-approved clinical criteria that was based on entry criteria for the clinical trials (11). It is therefore uncertain whether the clinical outcomes observed in experimental settings for DES are representative of those obtained in routine clinical practice. Therefore, the goals of this research were to measure the clinical outcomes of DES compared with BMS among a nationally representative cohort of elderly patients receiving PCI in nonexperimental settings.

Methods

Setting. The population for the study comprised Medicare beneficiaries ages 66 and older covered under fee-for-service Medicare. Medicare Part A (hospital) coverage is almost universal for Americans older than the age of 65 years, and more than 90% of elderly Americans are enrolled in fee-for-service Medicare; thus, this population is nearly ideal for investigations of national trends in health care. From among these Medicare beneficiaries (i.e., approximately 45 million persons), we identified patients with hospital claims indicating receipt of a DES between April 24, 2003 (the FDA approval date for DES), through December 2003, or receipt of a BMS from July 1, 2002, through December 31, 2003.

Patients with procedure codes indicating receipt of both stent types during the same hospitalization were excluded. We also excluded any patients who had prior Medicare claims indicating they had undergone PCI or coronary bypass surgery within the 6-month period before the "index" PCI that qualified the patient for inclusion in our study. Patients were only allowed to enter the cohort once—at their earliest PCI within the designated time windows. We only included patients ages 66 years and older, because many 65-year-old patients would not be expected to have had at least 6 months of previous Medicare coverage during which time information on prior procedures and comorbidities would have been recorded.

Comparison groups. For all qualifying DES and BMS recipients, we obtained data on age, race, and gender from the Medicare enrollment database. Information on clinical comorbidities and other cardiac diagnoses (e.g., acute myocardial infarction or acute coronary syndromes) was obtained from the hospitalization claim at the time of PCI (i.e., the index admission), as well as all other inpatient claims during the 6 months before the index hospitalization. We also determined whether each patient's index hospitalization had been classified as elective, urgent, or emergent. Information on the patient's PCI hospital, including geographic location and academic status (indicated by membership in the American Association of Medical College's Council of Teaching Hospitals and Health Systems), was obtained by linking each patient's hospital identifier to annual Hospital Cost Report Information System report data that are submitted annually to the Centers for Medicare and Medicaid Services by all hospitals participating in the Medicare program. The volume of Medicare admissions per calendar year for each admitting hospital was calculated using all Medicare acute-care hospitalization claims from 2002 to 2004.

All DES and BMS recipients were then combined in a single dataset, and a multivariate propensity score for receipt of DES was calculated for each patient using a multivariable logistic regression model with receipt of DES (vs. BMS) being the dependent variable, and the demographic, clinical, and hospital factors listed previously included in the model as independent variables (12). The propensity score is a well-validated statistical method designed to balance a large number of potential confounders equally across 2 observational cohorts of patients, without the traditional requirement of exactly matching patients 1-to-1 on each individual confounder (12,13).

We then matched each DES recipient to a BMS control patient by using a propensity score-matching optimization algorithm that selected an optimal match for each DES recipient among BMS patients with similar propensity scores (within 0.25 times the standard deviation of the propensity score logit) and having a minimum Mahalanobis distance calculated from key covariates (in this case, the covariates were age, diabetes, congestive heart failure, acute myocardial infarction, PCI at a high-volume center, and PCI at an academic center) (13). Because the pool of potential BMS controls receiving stents in the time period before FDA approval of the DES (April 2003), may have systematically differed in unobservable ways from the pool of potential BMS controls available after the FDA approval date, we matched DES patients separately to "contemporary" BMS controls, that is, BMS patients receiving stents during the same time interval (April to December, 2003) during which the DES patients received stents, as well as to "historical" controls, that is, BMS patients receiving stents during the 9 months immediately before the FDA approval of DES (July 2002 to March 2003). All subsequent analyses of clinical outcomes were made in parallel between these 2 pairs of matched DES-BMS cohorts.

Ascertaining clinical outcomes. Using the Medicare Denominator File, which is linked to the Social Security Administration's Death Master File and thus is a reliable indicator of mortality (14), we determined whether and when patients had died during the time interval from receipt

of PCI through December 31, 2005, the last available date in our database. We used inpatient claims in the Medicare database subsequent to the index stent receipt date to determine whether patients had been hospitalized with a diagnosis of acute myocardial infarction after receiving their stent and/or if they underwent additional coronary revascularization procedures after the initial PCI.

Statistical analyses. Standardized differences, calculated as percentages, were used to assess the quality of the propensity score match in reducing the potential for selection bias (13). The percent standardized difference is calculated by dividing the absolute difference in means by the pooled standard deviation. Standardized differences of <5% after a propensity score match are generally considered indicative of adequate matching on a particular variable (15).

Chi-square tests were used to compare differences in unadjusted outcomes ratios for DES recipients compared with BMS recipients. Cox proportional hazards survival models were fitted to compare mortality rates. Logistic regression was used to compare the odds of hospitalization for acute myocardial infarction, coronary revascularization, and the combined end point of mortality, coronary revascularization, or hospitalization for acute myocardial infarction at 1 and 2 years after PCI. The initial (unadjusted) models included only receipt of DES versus BMS as an independent variable. To further ascertain whether the propensity score match had successfully balanced covariates, as well as to control for residual confounding, we then fit these models with additional covariates, including the propensity score as well as all demographic, clinical, or hospital-level variables that were potentially not well-balanced (i.e., $p < 0.1$ for comparison of means) across subcohorts defined by quintiles of propensity scores. All data analyses were performed with SAS 9.1 (SAS Institute, Cary, North Carolina). A p value of 0.05 was considered statistically significant.

Results

Analytic cohorts: match quality. We identified 76,525 patients who received DES from April through December 2003. Of these patients, 71,965 (94%) were able to be matched to contemporary BMS controls, and all DES patients were able to be matched to historical BMS controls with the use of propensity score matching. There were differences in the age, race, geographic location, prevalence of selected cardiovascular diseases, and the prevalence of other clinical comorbidities between DES patients and all potential historical BMS controls (Table 1) as well as all potential contemporary BMS controls (Table 2). However, after implementation of the propensity score match and exclusion of unmatchable patients, subsequent comparisons of standardized differences in propensity scores, demographics, geographic factors, hospital factors, and clinical characteristics between propensity-score-matched DES and BMS cohorts revealed minimal residual differences in the distribution of covariates.

Analytic cohorts: descriptive statistics. Patients in the final (matched) analytic cohorts were predominantly white, the majority of patients were men, and the mean age was 75 years. Approximately 14% to 15% of patients had congestive heart failure, and approximately one-quarter of the patients had been hospitalized with acute myocardial infarction at the time of their coronary stent implantation. Slightly less than one-third of each cohort had diabetes. The majority of patients were admitted to high-volume (≥10,000 Medicare admissions per year) or moderate-volume (5,000 to 10,000 Medicare admissions per year) hospitals. Approximately one-half of each cohort was admitted to hospitals in urban areas, and approximately one-quarter of each cohort received PCI in academic hospitals. Patients in the DES cohort were followed for a mean of 2.3 years. Patients in the matched contemporary BMS cohort were followed for a mean of 2.4 years, whereas historical BMS controls were followed for a mean of 3.1 years.

Survival. Recipients of DES had significantly lower 90-day, 1-year, and 2-year unadjusted mortality compared with both matched contemporary BMS controls as well as matched historical BMS controls (Table 3). The absolute reduction in mortality at 2 years for DES patients was approximately 2% for the comparisons with both contemporary and historical controls. In Cox proportional hazards survival models that adjusted for the propensity score as well as for covariates that had residual, statistically significant differences across quintiles of propensity scores, DES receipt remained a significant predictor of improved survival compared with BMS receipt, with an adjusted hazard ratio of 0.83 (95% confidence interval 0.81 to 0.86) compared with contemporary controls, and an adjusted hazard ratio of 0.79 (95% confidence interval 0.77 to 0.81) compared with historical controls (Table 4). The 2 control groups were significantly heterogeneous ($p < 0.001$). Comparisons between unadjusted and adjusted coefficients and their confidence intervals indicated minimal differences, suggesting the propensity match had effectively balanced observed confounders. As a sensitivity analysis, we calculated "Rosenbaum bounds" for the minimum effect size of an unobserved variable necessary to confound the association between DES and survival (16). These calculations indicated the prevalence of such a factor must differ between DES and BMS patients by a minimum of a 16% standardized difference. By comparison, among the 25 observed variables included in our propensity match, only the prevalence of acute myocardial infarction differed by more than a 16% standardized difference between DES and BMS patients before matching.

Subsequent coronary revascularization procedures. Drug-eluting stent patients had lower rates of additional coronary revascularization procedures such as additional PCI procedures or subsequent coronary bypass surgery. Absolute differences in revascularization rates were approximately 2% when compared with contemporary controls and 3% compared with historical controls, within the first year, with the

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Table 1 Patients Receiving DES Compared With Historical BMS Controls*

Characteristic	Before Match			After Match		
	DES (n = 76,525)	BMS (n = 164,140)	Standardized Difference (%)†	DES (n = 76,525)	BMS (n = 76,525)	Standardized Difference (%)†
Logit of propensity score (SD)	−0.81 (0.27)	−0.88 (0.27)	26	−0.81 (0.27)	−0.82 (0.27)	1.2
Age, yrs, mean (SD)	75 (6)	75 (6)	7	75 (6)	75 (6)	0.1
Female	33,299 (44)	70,902 (43)	0.6	33,299 (44)	33,472 (44)	0.5
Race						
White	70,241 (92)	150,405 (92)	0.6	70,241(92)	70,188 (92)	0.3
Black	3,664 (5)	8,400 (5)	2	3,664 (5)	3,734 (5)	0.4
Other	2,620 (3)	5,335 (3)	0.6	2,620 (3)	2,603 (3)	0.1
U.S. Census region						
Northeast	15,625 (20)	27,621 (17)	9	15,625 (20)	15,864 (21)	0.8
Midwest	21,182 (28)	45,920 (28)	1	21,182 (28)	21,277 (28)	0.3
South	29,010 (38)	67,905 (41)	7	29,010 (38)	28,705 (38)	0.8
West	10,708 (14)	22,694 (14)	0.5	10,708 (14)	10,679 (14)	0.1
Cardiovascular disease						
Hypertension	47,208 (62)	95,755 (58)	7	47,208 (62)	46,970 (61)	0.6
Acute myocardial infarction	19,479 (26)	55,895 (34)	19	19,479 (26)	20,114 (26)	2
Congestive heart disease	10,725 (14)	26,183 (16)	5	10,725 (14)	10,814 (14)	0.3
Valvular heart disease	7,659 (10)	17,543 (11)	2	7,659 (10)	7,695 (10)	0.2
Peripheral vascular disease	7,372 (10)	16,056 (10)	1	7,372 (10)	7,348 (10)	0.1
Cardiac arrest or arrhythmia	3,226 (4)	9,054 (6)	6	3,226 (4)	3,226 (4)	0
Clinical comorbidity						
Diabetes	20,689 (27)	41,097 (25)	5	20,689 (27)	20,813 (27)	0.4
Chronic pulmonary disease	10,429 (14)	24,871 (15)	4	10,429 (14)	10,715 (14)	1
Cancer (no metastasis)	5,726 (8)	12,476 (8)	0.5	5,726 (8)	5,857 (8)	0.7
Hypothyroidism	5,844 (8)	12,135 (7)	0.9	5,844 (8)	5,831 (8)	0.1
Fluid or electrolyte disorder	3,293 (4)	8,538 (5)	4	3,293 (4)	3,412 (5)	0.7
Renal disease	1,738 (2)	4,257 (3)	2	1,738 (2)	1,805 (2)	0.6
Hospitalization in 90 days before PCI	10,896 (14)	24,561 (15)	2	10,896 (14)	11,040 (14)	0.5
Hospitalization in 270 days before PCI	24,884 (33)	56,051 (34)	3	24,884 (33)	25,022 (33)	0.4
Characteristics of PCI hospital						
Urban hospital‡	40,168 (52)	79,762 (49)	8	40,168 (52)	39,433 (52)	2
Academic hospital§	21,557 (28)	40,098 (24)	9	21,557 (28)	21,246 (28)	1
<5,000 admissions‖ per year	12,635 (17)	31,647 (19)	7	12,635 (17)	12,566 (16)	0.2
5,000 to 9,999 admissions‖ per year	35,426 (46)	76,588 (47)	0.7	35,426 (46)	35,361 (46)	0.2
≥10,000 admissions‖ per year	28,464 (37)	55,905 (34)	7	28,464 (37)	28,598 (37)	0.4

*All values given as n (%) unless otherwise indicated. Percentages may not add to 100 because of rounding. †The difference in means as a percent of the pooled standard deviation. ‡Hospital located in an urban county (U.S. Census definition). §Hospital was a member of the American Association of Medical College's Council of Teaching Hospitals and Health Systems. ‖Average Medicare admissions per calendar year, 2002 to 2004

BMS = bare-metal stent(s); DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

same absolute differences maintained in the second year. In multivariate analyses DES recipients had significantly lower adjusted odds of undergoing additional coronary procedures compared with both contemporary and historical BMS controls.

Major adverse clinical events. Patients who received DES had lower unadjusted hospitalization rates for acute myocardial infarction, with absolute differences ranging from 2% to 2.5%. Adjusted rates of hospitalization for subsequent acute myocardial infarction were likewise lower for DES patients compared with both contemporary and historical controls. In addition, DES patients had lower unadjusted and adjusted rates of the combined outcomes of hospitalization for acute myocardial infarction, coronary revascularization, or death compared to both historical and contemporary BMS control patients.

Subgroup analyses. We then fitted proportional hazards survival models that included age subgroups (ages 66 to 70, 71 to 75, 76 to 80, 81 to 85, and older than 85 years) as well as race and gender interacted with DES receipt. The only statistically significant interaction was for black patients in the comparison of DES recipients to contemporary BMS controls. The DES hazard ratio for black patients (0.89, 95% confidence interval 0.79 to 0.99) significantly differed

Table 2 Patients Receiving DES Compared With Contemporary BMS Controls*

Characteristic	Before Match			After Match		
	DES (n = 76,525)	BMS (n = 100,896)	Standardized Difference (%)†	DES (n = 71,965)	BMS (n = 71,965)	Standardized Difference (%)†
Logit of propensity score (SD)	−0.34 (0.43)	−0.52 (0.45)	41	−0.38 (0.41)	−0.38 (0.41)	1
Age, yrs, mean (SD)	75 (6)	75 (6)	11	75 (6)	75 (6)	0.6
Female	33,299 (44)	42,620 (42)	3	31,211 (43)	31,186 (43)	0.1
Race						
White	70,241 (92)	91,991 (91)	2	65,956 (92)	65,862 (92)	0.5
Black	3,664 (5)	5,580 (6)	3	3,580 (5)	3,689 (6)	0.7
Other	2,620 (3)	3,325 (3)	0.7	2,420 (3)	2,405 (3)	0.1
U.S. Census region						
Northeast	15,625 (20)	15,014 (15)	15	12,900 (18)	12,860 (18)	0.2
Midwest	21,182 (28)	29,829 (30)	4	20,382 (28)	20,757 (29)	1
South	29,010 (38)	42,483 (42)	9	28,579 (40)	28,281 (39)	0.8
West	10,708 (14)	13,570 (14)	2	10,095 (14)	10,058 (14)	0.2
Cardiovascular disease						
Hypertension	47,208 (62)	58,307 (58)	8	43,909 (61)	43,376 (60)	2
Acute myocardial infarction	19,479 (26)	38,023 (38)	27	19,479 (27)	20,783 (29)	4
Congestive heart disease	10,725 (14)	17,983 (18)	10	10,473 (15)	11,030 (15)	2.1
Valvular heart disease	7,659 (10)	11,103 (11)	2	7,341 (10)	7,437 (10)	0.4
Peripheral vascular disease	7,372 (10)	10,143 (10)	1	7,105 (10)	7,042 (10)	0.3
Cardiac arrest or arrhythmia	3,226 (4)	6,367 (6)	9	3,196 (4)	3,365 (5)	1
Clinical comorbidity						
Diabetes	20,689 (27)	24,913 (25)	5	19,163 (27)	18,889 (26)	0.9
Chronic pulmonary disease	10,429 (14)	16,528 (16)	8	10,096 (14)	10,609 (15)	2
Cancer (no metastasis)	5,726 (8)	7,659 (8)	0.4	5,338 (7)	5,352 (7)	0.1
Hypothyroidism	5,844 (8)	7,427 (7)	1	5,448 (8)	5,439 (8)	0.1
Fluid or electrolyte disorder	3,293 (4)	8,538 (8)	8	3,230 (5)	3,550 (5)	2
Renal disease	1,738 (2)	2,845 (3)	3	1,688 (2)	1,781 (3)	0.8
Hospitalization in 90 days before PCI	10,896 (14)	14,907 (15)	2	10,368 (14)	10,400 (15)	0.1
Hospitalization in 270 days before PCI	24,884 (33)	33,203 (33)	0.8	23,562 (33)	23,337 (33)	0.6
Characteristics of PCI hospital						
Urban hospital‡	40,168 (52)	46,516 (46)	13	36,542 (51)	36,177 (50)	1
Academic hospital§	21,557 (28)	22,226 (22)	14	18,649 (26)	18,936 (26)	1
<5,000 admissions‖ per year	12,635 (17)	22,993 (23)	16	12,633 (18)	12,033 (17)	2
5,000 to 9,999 admissions‖ per year	35,426 (46)	46,617 (46)	0.2	33,854 (47)	33,483 (47)	1
≥10,000 admissions‖ per year	28,464 (37)	31,286 (31)	13	25,469 (35)	26,440 (37)	3

*All values given as n (%) unless otherwise indicated. Percentages may not add to 100 because of rounding. †The difference in means as a percent of the pooled standard deviation. ‡Hospital located in an urban county (U.S. Census definition). §Hospital was a member of the American Association of Medical College's Council of Teaching Hospitals and Health Systems. ‖Average Medicare admissions per calendar year, 2002 to 2004.

Abbreviations as in Table 1.

(p = 0.04) from the DES hazard ratio for whites (0.78, 95% confidence interval 0.76 to 0.81). None of the other interactions were significant, suggesting the association between DES and improved survival was not modulated by age or gender.

Discussion

Among Medicare beneficiaries receiving PCI from mid-2002 to 2003, receipt of a DES was associated not only with a reduction in subsequent coronary revascularization procedures but also with a statistically significant reduction in mortality and fewer hospitalizations for subsequent acute myocardial infarction. This departure is a striking one from the results of both individual randomized controlled trials as well as pooled analyses from randomized trials, which have repeatedly demonstrated no statistical differences in survival or acute myocardial infarction between patients treated with DES versus BMS.

There are 2 nonexclusive possible explanations for these findings. The first is that receipt of DES, particularly "early" in the DES era (2003), was associated with factors that were not observable in our data but which conferred a significant survival benefit. This confounder (or set of confounders) would necessarily have a strong influence on the outcomes

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Table 3 Unadjusted Clinical Outcomes*

Time After PCI	DES	BMS	p Value
DES patients compared with matched contemporary BMS controls			
Mortality			
90 days	3.0	4.4	<0.001
1 yr	6.5	8.9	<0.001
2 yrs	10.7	13.5	<0.001
Hospitalization for subsequent AMI			
1 yr	7.2	9.3	<0.001
2 yrs	9.2	11.2	<0.001
Coronary revascularization			
1 yr	12.6	14.6	<0.001
2 yrs	17.2	19.1	<0.001
Combined end points†			
1 yr	21.7	26.2	<0.001
2 yrs	29.8	34.4	<0.001
DES patients compared with matched historical BMS controls			
Mortality			
90 days	2.9	3.7	<0.001
1 yr	6.2	7.9	<0.001
2 yrs	10.4	12.2	<0.001
Hospitalization for subsequent AMI			
1 yr	7.0	9.2	<0.001
2 yrs	8.9	11.4	<0.001
Coronary revascularization			
1 yr	12.6	15.7	<0.001
2 yrs	17.3	20.6	<0.001
Combined end points†			
1 yr	21.4	26.2	<0.001
2 yrs	29.5	34.5	<0.001

*Data are percentages. †Combined end point of mortality, AMI hospitalization, *or* coronary revascularization within the specified time period.
AMI = acute myocardial infarction; other abbreviations as in Table 1.

of mortality and subsequent myocardial infarction that would be protective among DES recipients and/or harmful among BMS recipients. It is possible that "healthier" patients (in ways not observable using administrative data) were preferentially selected for DES, such as patients with less-complex coronary lesions. Patients with DES may have been more likely to have been treated with antiplatelet agents such as clopidogrel, although clinical guidelines in 2003 did not favor clopidogrel use in DES over BMS recipients. Patients may have also been selected for DES who were more likely to be adherent to medications, although the clinical imperative for patient adherence to antiplatelet agents after DES was less apparent in 2003 than it is currently.

Patients receiving DES also may have had higher quality health care than patients receiving BMS, although if this were the case, a marked difference in the comparisons between contemporary and historical controls would be expected, because historical controls would have included the same "high-quality" physicians and hospitals that more rapidly adopted DES once this technology was available. Instead, we found remarkably little difference in the comparisons between DES and BMS patients, regardless of the control group used.

The second possibility is that DES may directly confer a clinical benefit that was not observed by the randomized clinical trials. This may be a function of statistical power: each of our analyses included approximately 150,000 patients, which is nearly 30 times larger than even the largest pool of clinical trial patients. As such, we had much greater power to detect small differences in outcomes. Furthermore, many clinical trials had very strict entry criteria and an extensive array of follow-up activities that may have attenuated a difference in clinical efficacy in the trial population. Another important difference between many of the randomized controlled trials and our cohort was the age of the patients—our cohort's mean age was 75 years, whereas only 3 of 14 clinical trials analyzed by Kastrati et al. (17) had mean ages exceeding 65 years. Our patient population had a greater baseline mortality and adverse clinical event rate than many of the clinical trial populations, thus potentially magnifying differences in the effectiveness of treatments. In fact, the observed mortality rate in our cohorts (6% to 9% per year) was substantially greater than the 1% annual

Table 4 Results of Multivariable Models: Clinical Outcomes*

	DES Compared With Contemporary BMS Controls		DES Compared With Historical BMS Controls	
Time Frame After PCI	Unadjusted	Adjusted	Unadjusted	Adjusted
Mortality				
N/A (hazard ratio)	0.84 (0.82–0.87)	0.83 (0.81–0.86)	0.79 (0.77–0.81)	0.79 (0.77–0.81)
Hospitalization for AMI				
1 yr	0.76 (0.73–0.79)	0.76 (0.73–0.79)	0.74 (0.71–0.76)	0.72 (0.69–0.75)
2 yrs	0.80 (0.77–0.83)	0.80 (0.78–0.83)	0.77 (0.74–0.79)	0.76 (0.73–0.78)
Coronary revascularization				
1 yr	0.84 (0.82–0.87)	0.84 (0.81–0.86)	0.78 (0.75–0.80)	0.77 (0.75–0.80)
2 yrs	0.88 (0.86–0.91)	0.87 (0.85–0.90)	0.81 (0.79–0.83)	0.80 (0.78–0.83)
Combined end points†				
1 yr	0.78 (0.76–0.80)	0.79 (0.77–0.81)	0.77 (0.75–0.79)	0.77 (0.75–0.78)
2 yrs	0.81 (0.79–0.83)	0.82 (0.80–0.83)	0.80 (0.78–0.81)	0.79 (0.78–0.81)

*Data are odds ratios (95% confidence intervals) unless otherwise indicated. †Combined end point of mortality, AMI hospitalization, or coronary revascularization within the specified time period.
Abbreviations as in Tables 1 and 3.

mortality rates observed in the SIRIUS (Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) (18), RAVEL (Randomized study with the sirolimus-eluting VELOCITY balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions) (19), and TAXUS-IV (In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation) (20) trials. It is also possible that the process of coronary restenosis, which has been observed in clinical trial populations as more common among BMS than DES recipients, was more likely to have adverse clinical consequences such as AMI or death among elderly patients than among the more robust, younger patients who were enrolled in clinical trials.

Comparisons with previous investigations. Spaulding et al. (21) pooled data from 4 clinical trials of sirolimus-eluting coronary stents versus bare metal stents (n = 1,748) and determined a 95% confidence interval for the mortality hazard ratio of 0.84 to 1.83. Similarly, Kastrati et al. (17) examined mortality among 4,958 patients in 14 randomized controlled trials and calculated a 95% confidence interval hazard ratio for mortality of 0.80 to 1.30. Our point estimates for mortality hazard ratio (0.79 compared with historical controls, 0.83 compared with contemporary controls) are nearly identical to the lower confidence boundary estimates for both of these studies.

In contrast to our findings, Lagerqvist et al. (22) reported a greater risk of death for DES recipients among 19,771 PCI recipients in Sweden from 2003 to 2004, also by using propensity score methods to improve adjustment for confounders, but without using matching and subsequent exclusion of poorly matched patients in the outcomes analysis. Use of this technique risks the inclusion of "outlier" patients who were poorly matched across treatments, thus increasing the potential bias in estimating the effect of DES (23). Our matched analyses excluded patients who were essentially unmatchable, thus reducing the potential for outliers to bias results.

DES Medicare analysis: limitations. This study was based on administrative claims data and thus is limited by the clinical detail such records inherently lack, including coronary anatomy, results of noninvasive testing, and cardiac functional status (e.g., echocardiography). Additionally, the Medicare claims we used for this study were solely derived from fee-for-service patients older than age 66 years; thus, our results may not apply to younger patients, or to patients covered by other types of insurance, including Medicare Advantage health maintenance organizations.

Detailed information about adjunctive therapy (including pharmacotherapy) for DES or BMS recipients was unavailable in this analysis of administrative claims data. It is therefore possible that patients receiving DES were more likely to receive other beneficial therapies such as aspirin, beta-blockers, and cholesterol reducing agents. Furthermore, recent evidence has suggested that maintenance of clopidogrel therapy after PCI may be more essential to reduce late adverse events for DES patients than for BMS patients. However, data on the importance of extended clopidogrel therapy for DES patients were not yet available during the time-frame of our study, in which all included patients received stents no later than December, 2003. It is also possible that patients with more complex coronary anatomy (e.g., ostial or bifurcation lesions) were selected to receive BMS even after DES were available. These lesions could have predisposed recipients to worse clinical outcomes, although published data supporting this is inconclusive.

A third limitation to our study is the lack of ideal comparison groups. Historical controls, even those who received their care with <12 months' difference in timing, may have received different quality health care in other domains as the result of ongoing enhancements in health care systems (e.g., quality management programs, electronic medical records, and so on). Furthermore, the manner in which patients were selected for PCI before the approval of DES may have systematically differed from the selection process once DES were available. Although we believe these selection pressures would have been less pronounced in the first 9 months after the new technology became available—practice patterns typically change gradually—the possibility that a "healthier" cohort of patients was being systematically selected for PCI after the appearance of DES on the market cannot be excluded. The comparison with contemporary controls may also select for those health systems, hospitals, and physicians that were quicker to adopt innovative methods, and/or that had more resources to invest in new technology. Both of these factors could be associated with improved survival among patients independent of whether patients received DES or BMS.

Although propensity score matching can simultaneously adjust for a multitude of factors that systematically differ between BMS and DES recipients and that also affect health care outcomes, it would not be effective at controlling for unmeasured differences (as hypothesized previously) that may not be correlated with the measured variables included in the propensity score model. Our sensitivity analyses indicated that the effect of a hypothetical, clinically important unmeasured variable would have had to be sizeable, and its difference in prevalence among DES and BMS patients would need to be extraordinary, to produce the observed difference in mortality that we observed between DES and BMS patients. Among the many factors we included in our propensity score models, only acute myocardial infarction—an "off-label" indication for DES—had such a pronounced prevalence difference among DES and BMS recipients before matching. We acknowledge it is not possible to definitively disprove the existence of a similar, unobserved confounder.

Implications. This study has important implications to policymakers continuing to face difficult decisions regarding the value of DES (24). One potential implication is that DES have previously unrecognized clinical value in reducing

mortality, although this effect may be confined to, or substantially more pronounced among, elderly patients. A second implication, even if there is actually no additional clinical benefit conferred directly by DES, is that there are substantial benefits conferred by hospitals and health care systems that adopt new cardiovascular technology more expeditiously. As the Centers for Medicare and Medicaid Services increasingly scrutinize the performance of hospitals and health care systems in terms of quality, an important marker for better outcomes may be the expeditious use of new technologies among clinically appropriate patients.

Conclusions

Among elderly Medicare beneficiaries treated with coronary stents between 2002 and 2003, receipt of DES was associated with a statically significant reduction in the rate of subsequent revascularization procedures, decreasing rates of subsequent hospitalization for acute myocardial infarction, and improved survival.

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